Annual Surveillance Summary: *Klebsiella* Infections in the Military Health System (MHS), 2015

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By Kristen Rossi and Uzo Chukwuma
EpiData Center Department
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Navy and Marine Corps Public Health Center
620 John Paul Jones Circle, Suite 1100
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14. ABSTRACT
This report provides an annual update for calendar year (CY) 2015 of previously reported retrospective data regarding Klebsiella infection burden among Military Health System (MHS) beneficiaries and Department of the Navy (DON) active duty (AD) service members with deployment-related infections. In 2015, the annual Klebsiella incidence rate (IR) for all MHS beneficiaries was 100.8 per 100,000 persons per year, reflecting a 24.6% increase of the weighted historic IR. The annual IR of multidrug-resistant (MDR) Klebsiella infections was 6.7 per 100,000 persons, or one-fifteenth the IR of non-MDR infections. Klebsiella infection burden was highest among females and the most frequent clinical presentation was urinary tract infection (UTI). Three-quarters of infections were community-associated (CA) cases, underscoring the need for research and surveillance assessing Klebsiella as a community-acquired infection. Elevated multidrug-resistant organism (MDRO) admission metrics indicated that a higher magnitude of MDR Klebsiella was imported into the MHS rather than pre-existing as a reservoir of infection. Viable treatment options remain for Klebsiella infections; low susceptibility to nitrofurantoin appears to conflict with high numbers of prescriptions for it.

15. SUBJECT TERMS
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Abstract

This report provides an annual update for calendar year (CY) 2015 of previously reported retrospective data regarding *Klebsiella* infection burden among Military Health System (MHS) beneficiaries and Department of the Navy (DON) active duty (AD) service members with deployment-related infections. In 2015, the annual *Klebsiella* incidence rate (IR) for all MHS beneficiaries was 100.8 per 100,000 persons per year, reflecting a 24.6% increase of the weighted historic IR. The annual IR of multidrug-resistant (MDR) *Klebsiella* infections was 6.7 per 100,000 persons, or one-fifteenth the IR of non-MDR infections. *Klebsiella* infection burden was highest among females and the most frequent clinical presentation was as a urinary tract infection (UTI). Three-quarters of infections were classified as community-associated (CA) cases, underscoring the need for research and surveillance assessing *Klebsiella* as a community-acquired infection. Elevated multidrug-resistant organism (MDRO) admission metrics indicated that a higher magnitude of MDR *Klebsiella* was imported into the MHS rather than pre-existing as a reservoir of infection. Viable treatment options remain for *Klebsiella* infections; however, low susceptibility to nitrofurantoin appears to be in conflict with high numbers of prescriptions for the antibiotic. These findings warrant continued surveillance to understand the evolving impact of *Klebsiella* within the MHS.

Contents

Background

Gram-negative bacterial infections caused by organisms in the genus *Klebsiella*, in the family Enterobacteriaceae, are among the most clinically significant nosocomial pathogens. In the United States (US), *Klebsiella* species are estimated to cause eight percent of all bacterial nosocomial infections, giving rise to a variety of severe diseases such as septicemia, pneumonia, and soft tissue infection.[1] Enterobacteriaceae organisms isolated from urinary tract infections (UTIs) are also described as pertinent pathogens associated with both community-acquired and hospital-acquired infections.[2] While *Escherichia coli* remains the principal pathogen isolated from UTIs, *Klebsiella pneumoniae* has been cited as the second most frequently identified organism. Recent results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) during 2009-2011 found 14.5% of all isolates collected from hospitalized patients with UTIs in the US were attributed to *K. pneumonia*, and almost 60% of these were classified as community-associated infections.[2]

Klebsiella spp. have the ability to harbor different mechanisms of resistance, rendering many commonly used antibiotics ineffective. Multi-drug resistant (MDR) *Klebsiella* infections have significantly impacted medical communities on a global scale and often leave only "last resort" antibiotics as treatment options. In recent decades, carbapenems were used with increased frequency as one of the few effective treatment options against drug-resistant, gram-negative organisms.[3] In the early 2000s, resistance to carbapenems emerged among Enterobacteriaceae organisms. Carbapenem-resistant Enterobacteriaceae (CRE), including *Klebsiella pneumoniae* carbapenemase (KPC), are unique among multidrug-resistant organisms (MDROs) because there are no reliable treatments to combat them, resulting in wide-ranging global public health implications.[4] Furthermore, bacteria with carbapenem-resistant genes typically confer resistance to additional antibiotic classes, resulting in a wide range of resistance patterns including extensively drug-resistant (XDR) organisms.[3] In US hospitals, the percentage of *Klebsiella* isolates that are carbapenem-resistant progressively increased from <1% in 2000 to 8% in 2006-2007 to 12% in 2009-2010.[5,6,7] In February 2015, the Centers for Disease Control and Prevention (CDC) reported the presence of CREs in 48 US states and endemic levels in South America, Europe, Africa, and Asia.[8]

During Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF), resistant gram-negative bacteria were identified in US combat support hospitals, and experts noted concern that the greater use of broad spectrum antibiotics to empirically treat casualties in the combat zone or along the evacuation chain would result in natural selection of more resistant pathogens.[9] Between 2002 and 2005, antibiotic susceptibilities declined for *K. pneumoniae* isolates collected in intensive care units and inpatient settings among soldiers returning home from OIF/OEF, and one military treatment facility (MTF) found antibiotic resistance to nearly all agents tested.[10] The United States Naval Ship (USNS) *Comfort* also reported MDR gram-negative infections at the beginning of OIF, the majority of which were reported among non-US trauma patients wounded in action. Although the proportion of *Klebsiella* infections isolated from all unique organisms on the USNS *Comfort* was small (6%), the isolates were highly resistant to third generation cephalosporins.[11]

In 2001, Jones et al. reported that nosocomial infections account for more than 77,000 deaths per year in the US, costing $5-$10 billion annually.[12] While gram-positive organisms have typically been the most frequent cause of nosocomial infections and continue to garner concern, gram-negative organisms have emerged with resistance at troubling rates.[12] In intensive care units, gram-negative bacteria have been identified, to varying degrees, as a frequent cause of the four most common types of healthcare-associated infections (HAIs): nosocomial pneumonia, UTIs, surgical site infections (SSIs), and blood stream infections (BSIs).[13] In 2003, among voluntarily participating US hospital intensive care units, *K. pneumoniae* was implicated in 7.2% of nosocomial pneumonia cases, 9.8% of UTIs, 3.0% of SSIs, and 4.2% of BSIs[13] A study assessing data from 2009-2010 reported that 8% of HAIs were due to *Klebsiella* spp., of which approximately 2% were caused by extended-spectrum cephalosporin-resistant species and less than 1% were carbapenem-resistant.[7]

Ongoing surveillance for *Klebsiella* is imperative to describe changing epidemiology and trends. This analysis presents an annual update for calendar year (CY) 2015 of *Klebsiella* infection burden among Military Health System (MHS) beneficiaries from previously reported retrospective data. This report describes the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for *Klebsiella* infections among MHS beneficiaries, as well as Department of the Navy (DON) active duty (AD) service members with deployment-related infections.

Methods

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducted retrospective surveillance of *Klebsiella* infection in the MHS in CY 2015 (01 January 2015 to 31 December 2015). Health Level 7 (HL7)-formatted Composite Health Care System (CHCS) microbiology data was used to identify positive *Klebsiella* laboratory results. A unique *Klebsiella* infection was defined as the first positive *Klebsiella* laboratory result per person per 30 days. Incidence represented the first unique infection per person per calendar year and prevalence was defined as all unique *Klebsiella* infections.

Demographic Classification

Demographic information for each incident infection was described using data within the HL7-formatted CHCS microbiology record and infections were classified according to the patient's gender, age, sponsor service (Air Force, Army, Marine Corps, or Navy), duty status (Active Duty, Retired, Family Member, or Other), and region of the facility where the specimen was collected. The Active Duty category included both active duty and recruit personnel, defined by the beneficiary type codes of 11 and 13, respectively.

Klebsiella incidence rates and prevalence infections were aggregated into six spatial regions and visualized as maps created in ESRI ArcGIS software (version 10.2.2). Organisms identified in each region may act as a reservoir within that region and contribute to the burden of exposure. Geographic regions were assessed within the continental United States (CONUS) and outside the CONUS (OCONUS), with the spatial regions identified as follows:

- **Northeast**: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey.
- **Midwest**: Michigan, Wisconsin, Minnesota, Ohio, Indiana, Illinois, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota.
- **West**: California, Oregon, Washington, Idaho, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Alaska, Hawaii.
- **South**: Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, Kentucky.
- **South Atlantic**: Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida.
- **OCONUS**: All US territories and non-US countries.[14]

Clinical Characteristics Classification

Clinical characteristics were described for prevalent infections using information within the HL7-formatted CHCS microbiology record. Specimens were classified as inpatient or outpatient based on the Medical Expense and Performance Reporting System (MEPRS) codes of the location where the specimen was collected. A MEPRS code of A indicated specimen collection in the inpatient setting. All other MEPRS codes were considered outpatient encounters.

Infections were classified into invasive and non-invasive categories using the specimen source or body site variables in the HL7-formatted CHCS microbiology record. The terms used to group the data into these categories are described in Table 1. In addition, infections were further categorized based on body collection sites specific to the organism of interest (e.g., urine, respiratory, bloodstream) to provide enhanced granularity to the source of infection. Clinical characteristics were presented as a proportion of all infections within the population meeting the definition criteria.

Table 1. Invasive and Non-Invasive Infection Classification for *Klebsiella* Infections Accessing the MHS

Infection Classification	If Body Site or Specimen Source Sample Taken From:
Invasive Infections	Blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, or synovial fluid
Other Non-Invasive Infections	Abscess, aspirate, body fluid, boil, bursa, carbuncle, cellulitis, cyst, discharge, drainage, exudate, eye, genital, lesion, pus, pustule, respiratory, skin, sputum, stool, swab, throat, tissue, urine, or wound

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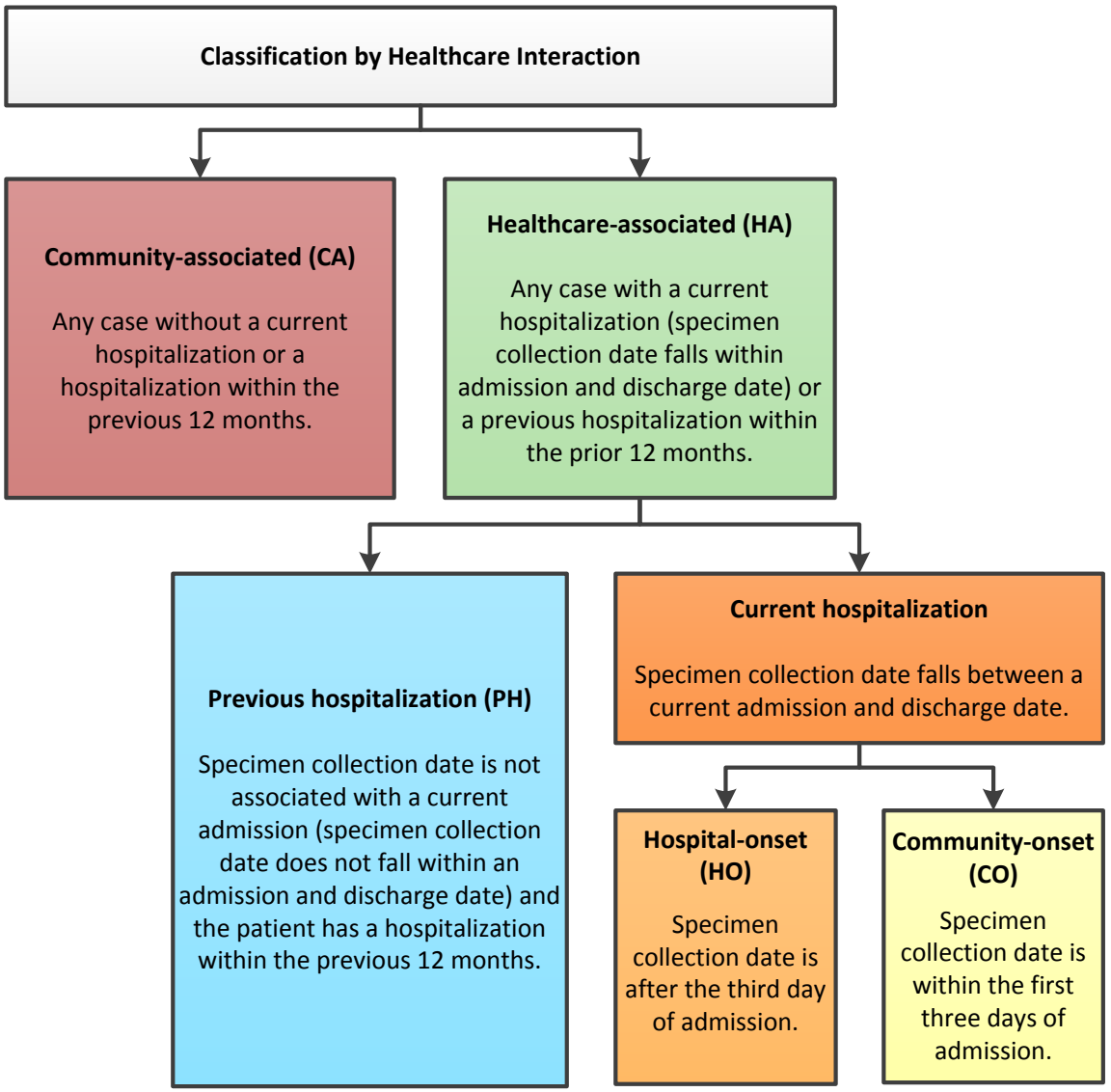
Epidemiologic Infection Classification

To evaluate all laboratory-confirmed *Klebsiella* infections for recent contact with the healthcare system, *Klebsiella* prevalence infections were matched to the Standard Inpatient Data Record (SIDR) to determine epidemiologic infection classification. Records were categorized as either community-associated (CA) or healthcare-associated (HA). CA cases were defined as patients without a current hospitalization nor a hospitalization in the previous 12 months. HA cases were defined as patients who were hospitalized at the time of infection (currently hospitalized) or who had a hospitalization within the previous 12 months. Current hospitalizations were further categorized as a hospital-onset (HO) case or a community-onset (CO) case. HO cases were defined as patients with a *Klebsiella* organism identified after the third day of the current admission. CO cases were identified as patients with a specimen collected within the first three days of the current admission yielding a *Klebsiella* organism, indicating the patient likely acquired the organism within the community and arrived at the treating facility with it.[15] Figure 1 presents the definitions for epidemiologic infection classifications.

Figure 1. Epidemiologic Infection Classifications[a]



[a]Cohen A, Calfee D, Fridkin SK, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infect Cont Hosp Ep*. 2008;29(10):901-913.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Only the first unique MDRO infection per patient per admission was used to analyze exposure burden metrics in the MHS. Admission prevalence estimated the exposure of infection at the time of admission (importation of MDROs into the MHS), which included MDROs isolated from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year. Overall prevalence included all individuals with

an MDRO infection identified from a sample collected at any point during the admission, or samples that tested positive for infection in the prior calendar year. Admitted patients with a history of colonization or infection were identified by searching prevalence infection MDROs from the prior calendar year to determine a history of infection. These beneficiaries were counted in both the admission and overall prevalence populations as they contributed to the colonization pressure and exposure burden for those not already colonized or infected in both populations.[15] The historical review of data is included to show a reservoir of antimicrobial resistance and pressure among *Klebsiella* infections. Regional rates of exposure burden were calculated as the rate of exposure (admission or overall prevalence) per 1,000 inpatient admissions per region per year.

Pharmacy Transactions

To analyze antimicrobial prescription practices in the MHS, the HL7-formatted microbiology *Klebsiella* prevalence infections were matched to pharmacy data to identify antibiotic prescriptions associated with *Klebsiella* infections in all pharmacy databases (outpatient oral (OP), inpatient oral (unit dose, or UD), and inpatient and outpatient intravenous (IV)). Prescriptions were considered to be associated with a *Klebsiella* infection if the transaction date in the pharmacy record occurred either seven days before or after the date the specimen was certified in the laboratory data. All pharmacy transactions, regardless of database source (UD, IV, OP), were evaluated as one data source. Cancelled prescriptions or those with zero or null filled prescriptions were removed prior to analysis. A unique antibiotic prescription was defined as the first dispensed prescription for an antibiotic per prevalence infection. Antimicrobials recommended for treatment of *Klebsiella* infections according to the Johns Hopkins Antibiotic Guide were retained for analysis.[16]

Antimicrobial Resistance Classification

To evaluate changes in antimicrobial susceptibility for *Klebsiella* infections, an antibiogram was created using antibiotic susceptibility results from the microbiology record according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[17] The antibiogram includes the first isolate per person per organism per year from 2010 to 2015. The Cochran-Armitage trend test was used to assess patterns in susceptibility across years. Trend direction for a single antibiotic over time was established using the two-tailed *P*-value; an increase in susceptibility was denoted by a green upward arrow and a decrease in susceptibility was denoted by a blue downward arrow. A statistically significant trend was established using a $P\text{-value} \leq .05$.

Susceptibility results from the microbiology record were used to establish the level of antibiotic resistance among prevalent infections. Specimens that were non-susceptible (resistant or intermediately susceptible) to at least one antibiotic from at least three different antibiotic classes were considered MDR. The antibiotic classes of interest in this classification included select cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, folate pathway inhibitors, glycylcyclines, monobactams, phenicols, phosphoric acids, penicillins and β-lactamase inhibitor combinations, polymyxins, and tetracyclines. Possible extensively drug-resistant (PXDR) infections were those organisms non-susceptible to some antimicrobials tested in an antimicrobial category but not tested against all antimicrobial categories in the definition and

could therefore not be included or excluded as an extensively drug-resistant (XDR) infection. Organisms that were non-susceptible to at least one antibiotic in all but two classes of sixteen total classes in the definition were considered XDR. Possible pandrug-resistant (PPDR) infections were those that could not be definitively identified as XDR based on the XDR definition and were non-susceptible to all antibiotics tested but were not tested against all antibiotics in the definition and could therefore not be excluded as a pandrug-resistant (PDR) infection. PDR organisms were organisms that were non-susceptible to all antibiotics in all antibiotic classes in the definition.[18] Carbapenem resistance, defined as antibiotic resistance to at least one carbapenem, was also evaluated.[19] MDR and CRE isolates were considered separately, therefore isolates could have been counted under both classifications. For the remainder of this report, unless otherwise stated, resistant and resistance are defined as *Klebsiella* infections having any level of antibiotic resistance, whether it be MDR, PXDR, XDR, PPDR, or PDR. See Appendix A (Table A1) for a list of antibiotics used to identify the level of resistance among infections.

Special Populations

Klebsiella infections identified among DON active duty personnel were matched to the Defense Manpower Data Center (DMDC) Contingency Tracking System (CTS) to explore deployment-related infections occurring on or between the start and end dates of the deployment plus 30 days. Thirty days post-end of deployment was used to ensure all *Klebsiella* infections related to the deployment were included. Records with no deployment end date (i.e., service member remains deployed) were also included provided that the infection occurred in the analysis year (2015) and the start date of deployment was within 180 days of the specimen certification date.

Statistical Analysis

The MHS Data Mart (M2) was used to obtain counts of TRICARE eligible MHS beneficiaries for denominators. The annual incidence rate was defined as the count of all incident infections per year divided by the corresponding annual M2 eligible beneficiary count (represented by the count in July) per year. A weighted average of incidence rates by month for the three years prior to the current analysis year (weighted historic monthly baseline) was used to assess the seasonal component of *Klebsiella* infections in 2015. One and two standard deviations, both above and below the weighted historic monthly baseline, were used to indicate statistically significant changes in incidence rates of *Klebsiella* infections in the analysis year.

All incidence rates are presented as an estimated rate per 100,000 persons per year. Due to the transient nature of the military beneficiary population and an inability to account for the proportion of the beneficiary population that receives medical care outside of the MHS, estimated rates are used for comparison of rates from year to year. A historical baseline was created using the weighted average of the immediately preceding three years. The historical baseline of the incidence rate serves as a clinical reference for the 2015 incidence rate. Two standard deviations on either side of the baseline were calculated to assess variation in incidence rate in the three years prior to the current evaluation period. Two standard deviations provide the upper and lower bounds (approximately 95%) for assessing whether the observed occurrence was likely due to chance, and for consideration of clinically significant trends.

Results

Section A – Descriptive Epidemiology

Incidence of *Klebsiella*

In 2015, the annual *Klebsiella* incidence rate (IR) for all MHS beneficiaries was 100.8 per 100,000 persons per year, reflecting a 24.6% increase above the weighted historic incidence rate, but within two standard deviations of the weighted historic incidence rate. Similar increases were demonstrated across all services, with service-specific trends remaining within two standard deviations of the respective weighted historic incidence rates. Incidence rates among DOD AD personnel demonstrated the largest increase by 28.0% from the weighted historic incidence rate of 74.7 per 100,000 persons to 95.6 per 100,000 persons per year; however, this trend also remained within two standard deviations of the weighted historic incidence rate. Across all populations analyzed, the 2015 IR was within two standard deviations of the weighted historic IR and therefore relatively stable to historical observations (Table 2).

Table 2. Incidence Rate (IR) for *Klebsiella* Infections in the MHS, CY 2015

Population	2015 IR	Weighted Historic[a] IR 2012 - 2014	Two Standard Deviations: Weighted Historic[a] IR	2015	
				Direction	Percent Change[b]
MHS Beneficiaries	100.8	80.9	22.2	↑	24.6%
Air Force	92.8	76.2	26.4	↑	21.8%
Army	101.5	80.6	20.8	↑	25.9%
Marine Corps	92.5	74.5	28.0	↑	24.1%
Navy	92.0	74.3	19.2	↑	23.7%
DOD Active Duty	95.6	74.7	21.4	↑	28.0%

Rates are presented as the rate per 100,000 persons per year.
A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.
[a] Historic IR reflects the weighted average of the three years prior to the analysis year.
[b] This reflects the percent change from the weighted historic IR to the IR of the current analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS Data Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Demographic Distribution of *Klebsiella*

In 2015, there were 9,504 incident infections of *Klebsiella* identified among all MHS beneficiaries accessing care at an MTF. Incidence rates among females (161.9 per 100,000 persons) exceeded the rates of males (41.7 per 100,000 persons) by approximately four times. By age group, incidence rates were relatively evenly distributed with the exception of those aged 0 to 17 years, who represented the lowest burden (29.8 per 100,000 persons). By beneficiary type, retirees demonstrated the lowest rates (53.4 per 100,000 persons) (Table 3).

Table 3. Demographic Characteristics of *Klebsiella* Infections in the MHS, CY 2015

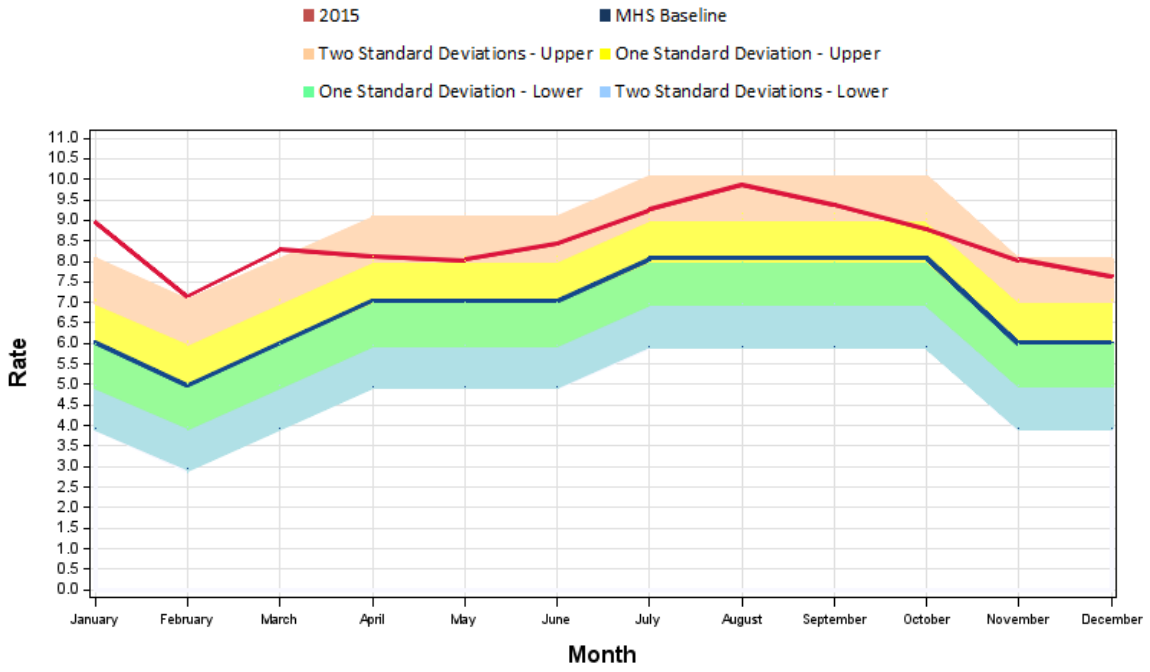
	N = 9,504	
	Count	**Rate**
Gender		
Female	7,504	161.9
Male	2,000	41.7
Age Group (in Years)		
0-17	586	29.8
18-24	1,394	120.6
25-34	1,316	109.7
35-44	986	118.2
45-64	2,556	122.6
65+	2,666	121.9
Beneficiary Type		
Active Duty	1,315	95.6
Family Members	6,237	113.0
Retired	1,157	53.4
Other[a]	795	--

Rates are presented as the rate per 100,000 persons per year.
[a] Rate is not reported due to variation in population denominator.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS Data Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Seasonality

During the first quarter of 2015, the *Klebsiella* annual incidence rate trended above expected variations, exceeding two standard deviations of the MHS baseline. For the remainder of 2015, the annual incidence rate was within two standard deviations of the MHS baseline. The elevated rates during the first quarter of the year may be attributed to the methodology, which defined incidence as the first unique infection per person per calendar year. Rates during 2015 were consistently higher during all months as compared to historical reference. Despite displaying an elevated burden above one standard deviation throughout the majority of the year, the 2015 rates followed trends exhibited by the weighted historic baseline; the 2015 rates peaked in August, during the highest trending rates for the weighted historic baseline between July and October (Figure 2).

Figure 2. Monthly Incidence of *Klebsiella* Infections and Baseline Comparisons in the MHS, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Bands indicate one and two standard deviations above and below the MHS baseline.
The MHS baseline is a weighted average of the three years prior to the analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS Data Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Klebsiella Clinical Characteristics

There were 10,569 prevalent *Klebsiella* infections identified among all MHS beneficiaries accessing care at an MTF in 2015. The largest proportion appeared in the outpatient setting (92.0%) and were non-invasive infections (91.9%). Almost 90 percent (87.4%) of *Klebsiella* prevalent infections were collected from urine; skin or soft tissue infections (SSTIs) and wounds yielded the second highest proportion (5.3%). The majority of prevalent infections were caused by *K. pneumoniae* (89.3%), followed by *K. oxytoca* (8.2%) (Table 4).

Table 4. Clinical Characteristics of *Klebsiella* Prevalence Infections in the MHS, CY 2015

	N = 10,569	
	Count	**Percentage**
Specimen Collection Location		
Inpatient	850	8.0
Outpatient	9,719	92.0
Infection Type		
Invasive	854	8.1
Other Non-Invasive	9,715	91.9
Body Collection Site		
Blood	156	1.5
Respiratory	325	3.1
SSTI/Wound	561	5.3
Urine	9,236	87.4
Other	291	2.8
Organism Species		
Klebsiella oxytoca	870	8.2
Klebsiella ozaenae	75	0.7
Klebsiella pneumoniae	9,440	89.3
Klebsiella rhinoscleromatis	2	0.0
Klesbiella species	182	1.7

Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Table 5 presents two different metrics defining MDRO infection rates for healthcare-associated exposures. During 2015, there were 252,751 inpatient admissions for beneficiaries across all MHS facilities. The overall MDRO prevalence rate for *Klebsiella* infections was 1.4 per 1,000 inpatient admissions; this measures the exposure of infection at any point during the admission or one year prior. The admission MDRO prevalence rate for *Klebsiella* spp. was slightly lower, at 1.2 per 1,000 inpatient admissions; this measures the magnitude of infection at the time of admission (importation into the healthcare system) or one year prior. The US Midwest region had the highest overall MDRO prevalence rate (2.1 per 1,000 inpatient admissions). With the exception of the US Northeast, all other regions demonstrated an overall MDRO prevalence rate between 1.1 and 1.4 per 1,000 inpatient admissions. Admission MDRO rates by region were comparable to overall MDRO rates, with the highest rate exhibited in the US Midwest (2.0 per 1,000 inpatient admissions), and all other regions demonstrated overall MDRO prevalence rate between 1.0 and 1.2 per 1,000 inpatient admissions (Table 5).

Table 5. MDRO Healthcare-associated Exposure Burden Metrics among *Klebsiella* in the MHS, CY 2015

	Overall MDRO Prevalence[a]		Admission MDRO Prevalence[b]	
	Count	Rate[c]	Count	Rate[c]
Region				
OCONUS	19	1.1	17	1.0
US Midwest	21	2.1	20	2.0
US Northeast	1	--	1	--
US South	79	1.3	68	1.2
US South Atlantic	109	1.3	98	1.2
US West	116	1.4	92	1.1
Total	345	1.4	296	1.2

[a] Overall MDRO prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.
[b] Admission MDRO prevalence included all individuals with an MDRO infection identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.
[c] Rates are presented as the rate per 1,000 inpatient admissions per year. Rates are not provided when the prevalence count is less than or equal to 5.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

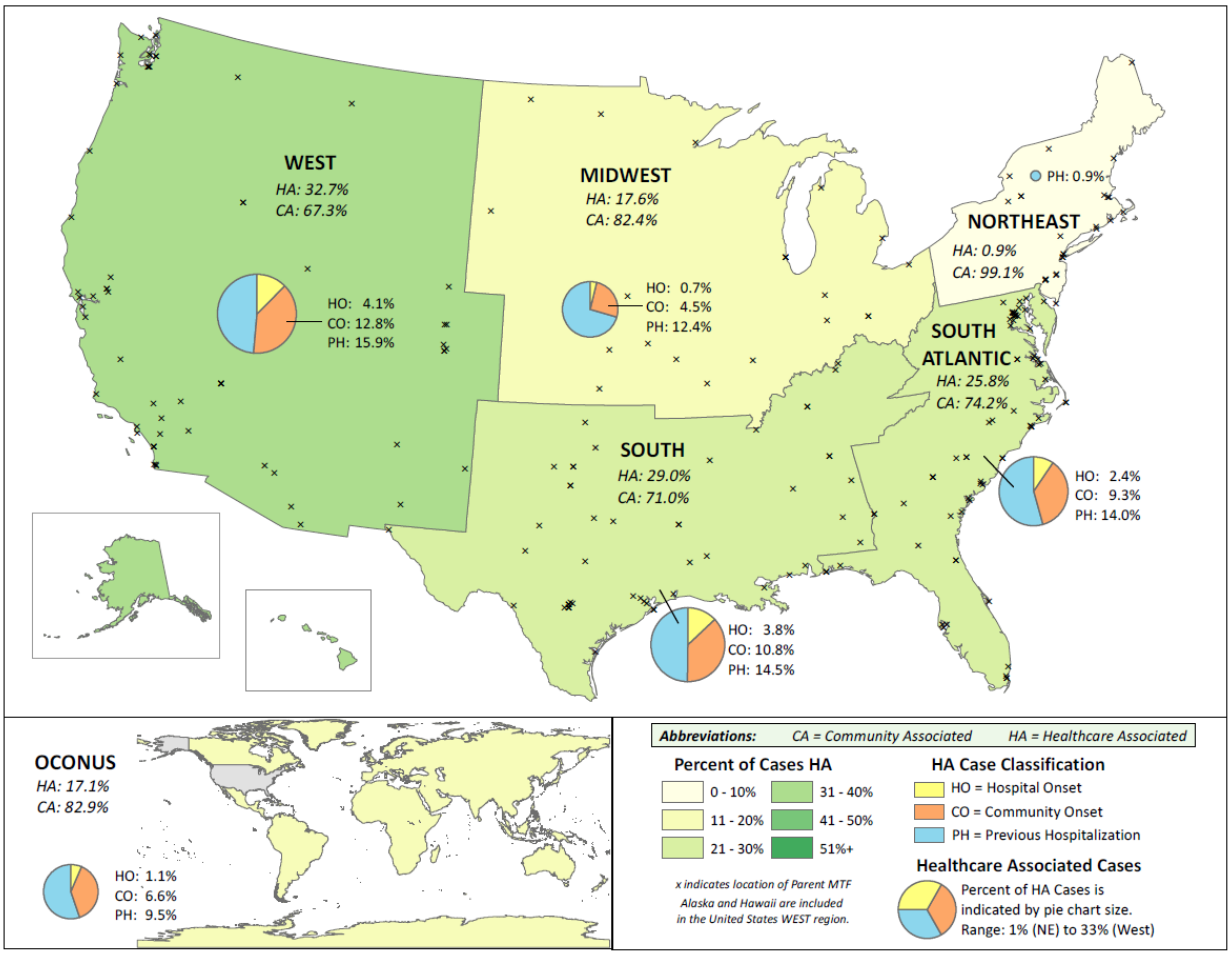
Regional Epidemiologic Infection Classifications

Among all *Klebsiella* prevalent infections identified in the MHS, 72.6% were CA cases and 27.4% were HA cases (data not shown). Regionally, the US West region reported the highest proportion of HA *Klebsiella* cases (32.7%), followed by the US South (29.0%), US South Atlantic (25.8%), US Midwest (17.6%), OCONUS locations (17.1%), and US Northeast (0.9%) (Figure 3).

HA cases were further categorized into hospital onset (HO), community onset (CO), or previous hospitalization (PH) classifications. Among the 2,897 prevalent *Klebsiella* infections identified as HA cases, the largest proportion were identified as PH (n=1,502; 51.8%), indicating the specimens were not associated with a current admission but that the patient had a prior hospitalization in the previous 12 months. The second largest proportion of HA cases were CO (37.1%; n=1,074), indicating the specimen was collected within the first three days of the hospital admission. Only 11.1% (n=321) of HA cases were HO, indicating the specimen was collected after the third day of admission, and therefore likely a result of the current hospitalization (data not shown).

By region, previous hospitalizations represented approximately half of all HA cases in the West, South, South Atlantic, and OCONUS regions. In the Midwest region, previous hospitalizations accounted for almost three-quarters of all HA cases. Only one HA case was identified in the Northeast region during 2015, which was classified as PH (Figure 3).

Figure 3. Proportion of Healthcare- and Community-Associated Cases among *Klebsiella* Infections in the MHS by Region, CY 2015



Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS Data Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section B – Antimicrobial Resistance and Use

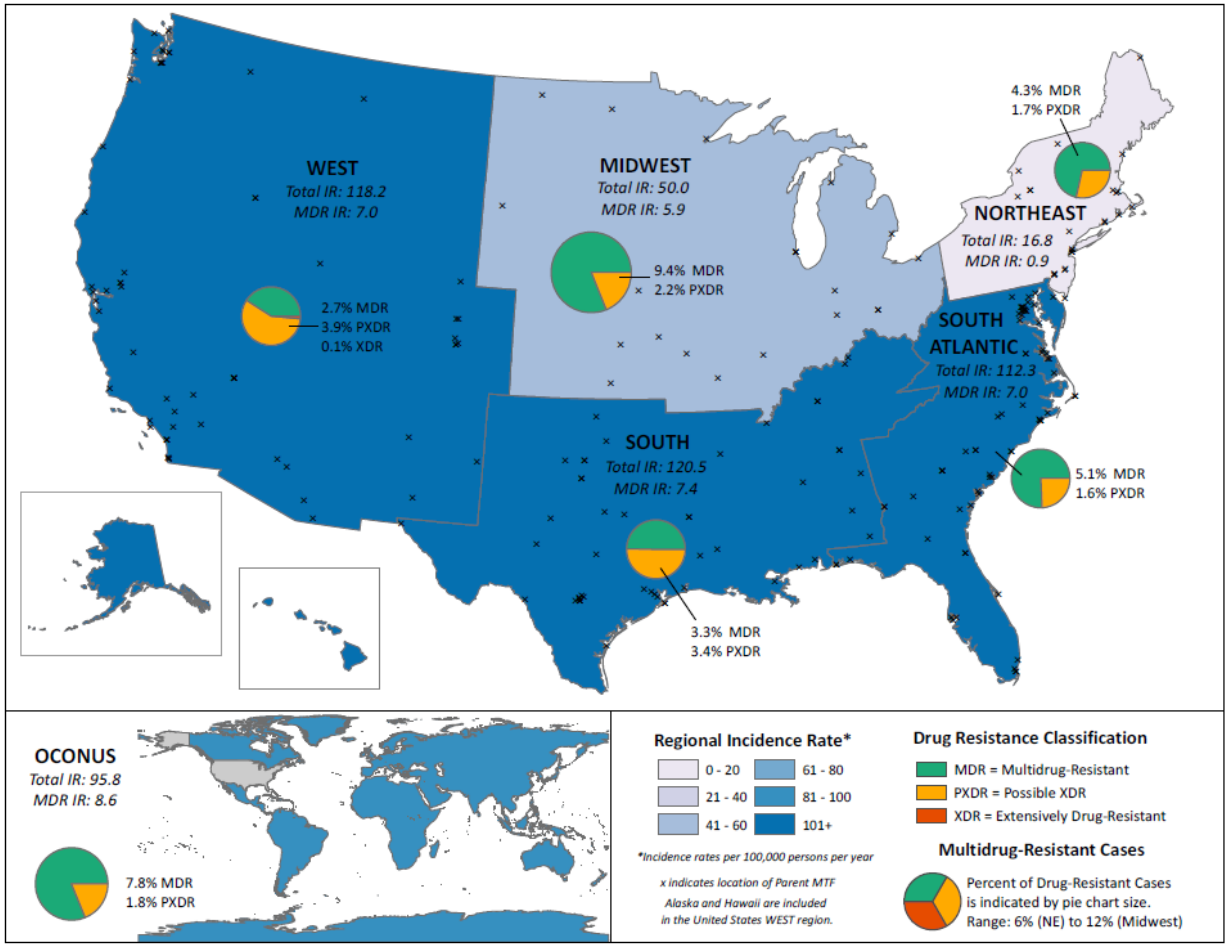
Regional Multidrug Resistance

The 2015 MDR *Klebsiella* incidence rate (6.7 per 100,000 persons) was approximately one-fifteenth of the total annual *Klebsiella* incidence rate (100.8 per 100,000 persons) among all MHS beneficiaries (data not shown). With the exception of the OCONUS rates, regions with the highest total incidence rates also represented those areas experiencing the highest MDR incidence rates. The West (118.2 per 100,000 persons), South (120.5 per 100,000 persons), and South Atlantic regions (112.3 per 100,000 persons) accounted for the top three regional incidence rates and MDR rates between 7.0-7.4 per 100,000 persons, whereas the OCONUS region had a lower incidence rate (95.8 per 100,000) and an MDR rate of 8.6 per 100,000 persons. The Midwest and Northeast regions accounted for the lowest *Klebsiella* incidence rates by region (50.0 per 100,000 persons and 16.8 per 100,000 persons, respectively), as well as the lowest MDR rates (5.9 per 100,000 persons and 0.9 per 100,000 persons, respectively) (Figure 4).

Prevalent drug-resistant *Klebsiella* infections are further categorized by drug-resistance type; among the 752 drug-resistant prevalent infections identified during 2015, 61.0% (n=459) are classified as MDR, 38.4% as PXDR (n=289), and 0.5% (n=4) as XDR (data not shown). These three drug-resistant *Klebsiella* classifications are described as a proportion of all prevalent infections by region in Figure 5. The West accounts for the largest proportion of prevalent infections classified as PXDR (3.9%), followed by the South (3.4%), and Midwest (2.2%) regions. The OCONUS (1.8%), Northeast (1.7%), and South Atlantic (1.6%) regions each accounted for less than two percent of prevalent infections classified as PXDR (Figure 4).

Prevalent *Klebsiella* infections were also assessed for carbapenem resistance. Of the 10,569 prevalent infections identified among MHS beneficiaries in 2015, 0.2% (n=23) were classified as CRE. Notably, only five CRE *Klebsiella* infections were identified in 2014; however, 18 infections were identified in 2013, indicating variable trends over the past three years. The majority of the carbapenem-resistant *Klebsiella* infections during 2015 occurred among beneficiaries in the West (n=12), followed by those in the South Atlantic (n=4). Two infections were identified in each of the Midwest, South, and OCONUS regions, and one infection was identified in the Northeast (data not shown).

Figure 4. Annual Incidence Rate (IR) and Percentage of Multidrug Resistance among *Klebsiella* Infections in the MHS by Region, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS Data Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antibiogram

Table 6 displays an antibiogram of *Klebsiella* infections for all MHS beneficiaries from 2010 through 2015. In 2015, *Klebsiella* infections were susceptible to a wide range of antibiotics, with susceptibility above 99% for doripenem (100.0%), ertapenem (99.6%), imipenem (99.4%), meropenem (99.4%), and amikacin (99.3%). Infections were less than 90% susceptible to ampicillin/sulbactam (85.8%) and nitrofurantoin (41.5%). Statistically significant decreases in efficacy were observed among ampicillin/sulbactam, imipenem, and nitrofurantoin, whereas significant increasing trends in efficacy were observed in aztreonam and ciprofloxacin (Table 6).

Table 6. Antibiogram of *Klebsiella* Infections Identified in the MHS, CY 2010-2015

Antibiotics	2010	2011	2012	2013	2014	2015	Susceptibility Trend	Comment[a]
Amikacin	99.5	99.5	99.4	99.5	99.7	99.3		
Amoxicillin/ Clavulanate	96.2	95.9	96.0	96.4	96.0	96.5		
Ampicillin/ Sulbactam	86.6	87.6	88.1	86.7	85.8	85.8		↓
Aztreonam	94.2	95.8	95.2	95.6	97.3	96.8		↑
Cefepime	98.2	98.1	98.5	98.6	98.1	97.8		
Cefotaxime	98.9	98.8	98.2	98.4	97.7	98.0		
Cefpodoxime	99.1	99.3	95.9	98.3	97.1	--		
Ceftazidime	98.4	97.9	98.4	98.4	98.3	98.3		
Ceftriaxone	97.2	97.5	98.2	98.1	97.7	97.6		
Cefuroxime	95.7	95.2	94.0	94.4	94.4	95.0		
Ciprofloxacin	96.9	96.9	97.4	97.5	97.7	97.5		↑
Doripenem	--	--	--	100.0	100.0	100.0		
Ertapenem	99.6	99.8	99.9	99.4	99.8	99.6		
Fosfomycin	--	--	--	--	--	--		
Gentamicin	98.2	98.6	98.8	98.6	98.5	98.4		
Imipenem	99.8	99.5	99.7	99.4	99.7	99.4		↓
Levofloxacin	98.3	98.2	98.3	98.0	98.4	98.2		
Meropenem	99.6	99.7	99.4	99.9	99.8	99.4		
Nitrofurantoin	44.2	42.4	38.7	37.9	38.0	41.5		↓
Piperacillin/ Tazobactam	95.2	96.9	96.8	96.9	96.3	96.1		
Tobramycin	97.5	97.7	98.1	98.2	97.6	97.7		

'--' indicates that fewer than 30 isolates were tested.

[a] Arrow indicates the antibiotics with a significant change in direction of trend for significant two-tailed Cochrane-Armitage tests for trend established for a single antibiotic over time. A significant increase in susceptibility is denoted by a green upward arrow and a significant decrease in susceptibility is denoted by a blue downward arrow.

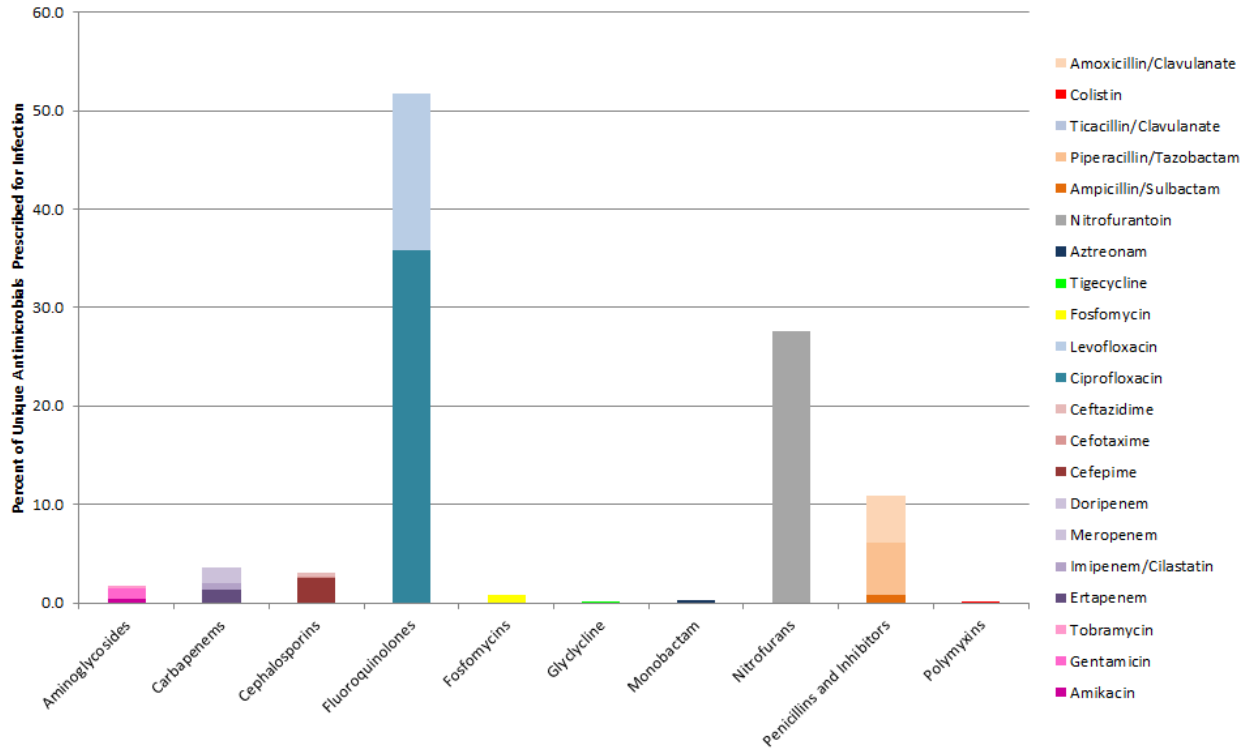
Data Source: NMCPHC HL7-formatted CHCS microbiology database.

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antimicrobial Consumption/Prescription Practices

Figure 5 displays the percentage of antimicrobials prescribed for *Klebsiella* infection during 2015. Among all MHS beneficiaries, the most commonly prescribed antibiotic classes for *Klebsiella* infections in 2015 were fluoroquinolones (51.8%), nitrofurans (27.6%), and penicillins and inhibitors (10.9%). Within the fluoroquinolone class, ciprofloxacin (35.8%) and levofloxacin (16.0%) were prescribed. Among penicillins and inhibitors, piperacillin/tazobactam (5.4%), amoxicillin (4.7%), and ampicillin (0.8%) were prescribed (Figure 5).

Figure 5. *Klebsiella* Infection and Prescription Practices in the MHS, CY 2015



Only the first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route.
Data Source: NMCPHC HL7-formatted CHCS microbiology and HL7-formatted pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section C – Special Populations

In 2015, there were 19 deployment-related infections among 478 prevalent *Klebsiella* infections in DON active duty personnel. Of these 19 deployment-related *Klebsiella* infections, eight were male and 11 were female. DON deployment-related infections were distributed across all age groups, with seven occurring among personnel aged 18-24 years, seven among personnel aged 35-44 years, four among personnel aged 35-44 years, and one infection in personnel aged 45-64 years.

Discussion

This report describes a recent increase in *Klebsiella* infection rates from the historic baseline of 80.9 infections per 100,000 persons to 100.8 infections per 100,000 persons in 2015. Upward trends were observed among beneficiaries from all services, with a notable increase in DOD active duty personnel. The upward trend in *Klebsiella* infection rates among MHS beneficiaries was also observed last year, when rates increased by 33% from 2013 to 2014. Prior to that, *Klebsiella* infection rates demonstrated a consistent downward trend from 2007 to 2013.[20]

Assessment of clinical and demographic characteristics found that UTIs were the most common manifestation of *Klebsiella* infections, and rates were highest among women. These results are consistent with other literature citing that *Klebsiella* spp. account for 6-15% of all inpatient and outpatient UTIs, and women are significantly more likely to experience a UTI than men.[21,22] *Klebsiella* infections among females of reproductive age may be captured at higher rates than other populations, as the US Preventive Services Task Force and the Infectious Disease Society of America recommend screening for asymptomatic bacteriuria among pregnant women and those undergoing urologic procedures.[23,24] Additional sub-analyses by gender and age would be required to further define the rates for child-bearing females compared to their male counterparts. This analysis demonstrated that *Klebsiella* incidence rates were distributed relatively evenly throughout all age groups, with the exception of beneficiaries less than 17 years of age who accounted for the lowest burden. The presence of infection in the 0-17 age category is not without consideration. UTIs in children can cause long-term medical sequelae, requiring prompt diagnosis and management to prevent subsequent complications.[25]

In the community setting, *K. pneumoniae* maintains the potential for various clinical manifestations, including septicemia, pneumonia, UTIs, meningitis, and purulent abscesses. *K. pneumoniae* has long been recognized as a pulmonary pathogen, but little research documents the host and virulence factors related to community-acquired *Klebsiella* from UTIs.[21] While the classic community-acquired pneumonia no longer persists outside of Africa and Asia, one study attributes community-acquired *Klebsiella* bacteremia to UTIs and vascular catheter infections in the US, Europe, Argentina, and Australia.[26] This analysis corroborated this finding, as the majority of *Klebsiella* infections identified in the MHS during 2015 were collected from urine specimens, and almost three-quarters were categorized as CA cases. This underscores the need for surveillance of *Klebsiella* risk factors defining community-associated infection, in addition to healthcare-associated infections. Furthermore, studies have documented diabetes mellitus as an underlying condition with community-acquired *K. pneumoniae* UTIs, as well as recurrent UTIs associated with *K. pneumoniae* in older females.[26,27] Future assessments of *K. pneumoniae* UTI and recurrent UTIs in MHS beneficiaries, stratified by age, gender, and underlying conditions, may be warranted.

MDR *Klebsiella* infections occurred far less frequently than non-MDR *Klebsiella*, where the annual MDR rate (6.7 per 100,000 persons) was approximately one-fifteenth of the total *Klebsiella* incidence rate (100.8 per 100,000 persons). With the exception of OCONUS locations, regions with the highest total incidence rates also represented those with the highest MDR incidence rates; the US West, US South, and US South Atlantic regions accounted for the

top three regional incidence rates and MDR rates between 7.0-7.4 per 100,000 persons, whereas the OCONUS region had the fourth highest regional incidence rate and an MDR rate of 8.6 per 100,000 persons.

Analyses defining MDRO healthcare-associated exposure burden metrics implicate community acquisition of drug-resistant *Klebsiella* across each region. While the overall MDRO prevalence rate measured the reservoir of drug-resistant *Klebsiella* infection in a healthcare setting, the admissions MDRO prevalence metric measured the magnitude of drug-resistant *Klebsiella* imported into the healthcare system. Because the admissions prevalence metric contributes to the overall prevalence metric, this analysis feasibly demonstrated that a large proportion of MDRO *Klebsiella* infections are imported into the healthcare system; the admissions prevalence rate during 2015 (1.2 per 1,000 inpatient admissions) accounted for approximately 85% of the overall prevalence metric (1.4 per 1,000 inpatient admissions). With the exception of the US Northeast, elevated MDRO prevalence admissions rates were observed across all regions. These results underscore the need for drug-resistance surveillance outside of traditional hospital settings.

Klebsiella isolates retained high susceptibilities to many tested antibiotics, indicating a range of viable treatment options for infections. Nitrofurantoin accounted for one of three antimicrobials that significantly decreased in efficacy over the surveillance period, maintaining the lowest efficacy in 2015. These results are noteworthy, as analysis also identified a large proportion of nitrofurantoin prescriptions during 2015 for treatment. Johns Hopkins recommends nitrofurantoin for uncomplicated UTIs caused by *Klebsiella*; however, the relationship may require investigation.[16] Further assessments may be warranted to describe the occurrence of nitrofurantoin treatment followed by another recommended regimen for *Klebsiella* infections, as some physicians could be empirically treating for UTIs thought to be caused by *Escherichia coli*, which accounts for roughly 80% of CA UTIs.[28,29] Ciprofloxacin and levofloxacin represent two additional antimicrobials most prescribed for *Klebsiella* infections in this assessment, which are also recommended as oral doses by Johns Hopkins for mild to moderate, community-acquired infection of uncomplicated UTIs, or as intravenous regimens for severe, nosocomial infections without the risk of methicillin-resistant *Staphylococcus aureus*.[16]

In summary, this report documents a continued, upward trend for *Klebsiella* infection rates among MHS beneficiaries since 2014. The characteristics of infections in 2015 are concurrent with existing literature that reports a higher burden among females and clinical presentation as UTIs. Three-quarters of infections were classified as CA cases, underscoring the need for research and surveillance assessing *Klebsiella* as a community-associated infection. Furthermore, the elevated MDRO admission metrics indicate a higher magnitude of MDR *Klebsiella* is imported into the MHS rather than pre-existing as a reservoir. Finally, analysis of antibiotic susceptibility patterns indicated that viable treatment options are still present for *Klebsiella* infections; however, the low efficacy of nitrofurantoin appears to conflict with the high numbers of nitrofurantoin prescriptions and may warrant further investigation.

Limitations

HL7-formatted data are generated within the CHCS at fixed MTFs; therefore, this analysis does not include microbiology records from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities.

Microbiology data are useful for identifying laboratory-confirmed infections. However, infections that were treated presumptively without laboratory confirmation do not exist in the microbiology data. Clinical practice with regards to culturing varies between providers and facilities. Examples of situations where cultures may not be performed include confirmatory tests for patients with influenza-like illness (ILI) symptoms, or patients with superficial infections who are treated presumptively. Therefore, infection counts identified here may be an underestimate of the actual burden of *Klebsiella* in the MHS.

The data restructuring process for the analysis of clinical characteristics and antimicrobial resistance does not capture non-standard CHCS records. These non-standard records may include those containing the results of tests performed at reference laboratories or novel organism antibiotic combinations. The use of microbiology data for analysis of antibiotic resistance is also limited by the practice of cascade reporting, in which antibiotic sensitivity results are conditionally reported in CHCS to guide antimicrobial selection and treatment decisions. Cascade reporting is practiced to varying degrees at MHS MTFs.

The EDC data feed does not include records on medical encounters conducted outside the MHS (e.g., purchased care in the community) and it cannot be determined if an individual truly had no healthcare contact or other risk factors for *Klebsiella* infection, or if the individual had a risk factor that was not visible in the available data. Data on other factors commonly used to define HA infections were not available (e.g., presence of an invasive device, history of dialysis or surgery, a long-term care facility stay in the 12 months preceding the culture). Therefore, there may be HA infections currently miscategorized as CA infections. Without the ability to identify these HA infections, a more accurate estimate of CA infections could not be determined. Given the relatively healthy military population, however, any misclassification bias is likely minimal.

The pharmacy databases consist of outpatient non-intravenous prescriptions (outpatient), inpatient non-intravenous prescriptions (unit dose), and intravenous prescriptions (intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received.

It is possible that not all antibiotic prescriptions were dispensed in response to a *Klebsiella* infection. Antibiotics that were prescribed within the appropriate timeframe to be associated with a *Klebsiella* specimen collection date may have actually been provided for reasons other than the documented infection, such as a different infection occurring after *Klebsiella* was isolated.

However, most antibiotics identified as being associated with a *Klebsiella* infection were antibiotics that are typically used to treat *Klebsiella*, so it is likely that the majority of prescriptions in this analysis were truly in response to the *Klebsiella* infection.

DMDC provides monthly snapshots of each active duty, reserve, and deployed Navy and Marine Corps service member's personnel record. Data are provided to DMDC by the service and analyses are dependent on the quality and completeness of these data. Any changes in service member status after the monthly data are extracted will not be captured until the following month. Active duty and reserve personnel records are maintained in separate databases, but activated reservists may be captured in the active duty DMDC file rather than the reserve DMDC file. Unit Identification Codes (UICs) reported for Marine Corps service members represent Reporting Unit Codes (RUCs), rather than UICs.

Personnel records for deployed service members are provided via CTS. The purpose of DMDC CTS is to capture personnel information for Central Command (CENTCOM) deployments. Additionally, deployment start and end dates are derived from the following systems and may not reflect the actual dates of deployment: Defense Finance Accounting System (DFAS), the Deployed Theater Accountability System (DTAS), the Secure Personnel Accountability System (SPA), historical PERSTEMPO files, and the Individual Personnel TEMPO Program. A country location of ZZ may represent shipboard or an unknown deployment location.

Infections may not be uniformly distributed within a spatial region; no distinctions were made with regard to the heterogeneity of incidence rates or prevalence among subunits (e.g., states, non-US countries). The choropleth maps represent an annual snapshot of infections and do not reflect the geographic movement of service members within the course of a year. Infections were georeferenced according to the locations of the MTFs where they were encountered, not according to the deployment locations or home locations of the service members. Map area does not equate to population size; parent MTF locations are displayed within US regions to convey the density of military medical facilities within each region.

POINT OF CONTACT

Navy and Marine Corps Public Health Center
Hospital Associated Infections and Patient Safety Division
EpiData Center Department 757.953.0970
WWW.NMCPHC.MED.NAVY.MIL/
usn.hampton-roads.navmcpubhlthcenpors.list.nmcphc-epi-datactr@mail.mil

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Appendix A: Antibiotics Included in the Resistance Definitions

Table A1. Antibiotics Included in the Resistance Definitions for *Klebsiella* spp. in the DOD, CY 2015

Antibiotic Class	Antibiotics Inlcuded in Class
Aminoglycosides	Amikacin
	Gentamicin
	Netilmicin
	Tobramycin
Anti-MRSA cephalosporins[a]	Ceftaroline
Antipseudomonal penicillins & β-lactamase inhibitors	Piperacillin/Tazobactam
	Ticarcillin/Clavulanic Acid
Carbapenems	Doripenem
	Ertapenem
	Imipenem
	Meropenem
1st & 2nd Generation Cephalosporins (non-extended specturm cephalosporins)	Cefazolin
	Cefuroxime
3rd & 4th Gneration Cephalosporins (Extended spectrum cephalosporins)	Cefotaxime or ceftriaxone
	Ceftazidime
	Cefepime
Cephamycins	Cefoxitin
	Cefotetan
Fluoroquinolones	Ciprofloxacin
	Levofloxacin[c]
Folate pathway inhibitors	Trimethoprim/Sulfamethoxazole
Glycylcyclines	Tigecycline
Monobactam	Aztreonam
Penicillins & β-lactamase inhibitors	Amoxicillin/Clavulanic Acid
	Ampicillin/Sulbactam
Phenicols	Chloramphenicol
Phosphoric Acid	Fosfomycin
Polymyxins	Colistin
Tetracyclines	Doxycycline
	Minocycline
	Tetracycline

[a] Included only for *Klebsiella pneumoniae* and *K. oxytoca*.
Source: Magiorakos et al., 2012.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Appendix B: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
BSI	bloodstream infection
CA	community-associated
CDC	Centers for Disease Control and Prevention
CENTCOM	Central Command
CHCS	Composite Health Care System
CLSI	Clinical and Laboratory Standards Institute
CO	community-onset
CONUS	continental United States
CRE	carbapenem-resistant Enterobacteriaceae
CTS	Contingency Tracking System
CY	calendar year
DFAS	Defense Finance Accounting System
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DON	Department of the Navy
DTAS	Defense Theater Accountability System
EDC	EpiData Center Department
HA	healthcare-associated
HAI	healthcare-associated infection
HICPAC	Hospital Infection Control Practices Advisory Committee
HL7	Health Level 7 format
HO	hospital-onset
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
M2	Military Health System (MHS) Management Analysis and Reporting Tool
MDR	multidrug-resistant
MDRO	multidrug-resistant organism
MEPRS	Medical Expense and Performance Reporting System
MHS	Military Health System
MTF	military treatment facility
NMCPHC	Navy and Marine Corps Public Health Center
OCONUS	outside the continental United States
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OP	outpatient oral
PDR	pandrug-resistant
PPDR	possible pandrug-resistant
PXDR	possible extensively drug-resistant
PH	previous hospitalization
RUC	reporting unit code
SIDR	Standard Inpatient Data Record
SMART	Study for Monitoring Antimicrobial Resistance Trends

Acronym/Abbreviation	Definition
SPA	Secure Personnel Accountability System
SSI	surgical site infection
UD	unit dose
UIC	unit identification code
US	United States
USNS	United States Naval Ship
UTI	urinary tract infection
XDR	extensively drug-resistant